INVESTIGATOR EDUCATION FOR THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Clinical Investigation & Research Department
Naval Medical Center
Portsmouth, Virginia

Investigator Education for the
Protection of Human Research Participants
Clinical Investigation and Research Department
Naval Medical Center, Portsmouth (NMCP)

The responsible conduct of research includes not only knowledge of sound methodological and scientific principles, but concepts, principles and issues related to the protection of human participants in research studies. The importance of conducting research in a way that promotes the rights and welfare of human participants in research cannot be overstated.

Federal regulations require institutions that conduct research involving human subjects to provide in writing, the procedures it will use to protect the rights and welfare of human subjects. In lieu of these written assurances, institutions may accept the existence of a current assurance on file with the Office of Human Research Protections (OHRP – formerly OPRR – Office for Protection from Research Risks) in the Department of Health and Human Services (HHS). This is commonly referred to as Federal Wide Assurances (FWA).

These assurances commit all NMCP employees to comply with policies for the protection of human subjects before initiation of any research and to continue compliance throughout the conduct of the study. Failure to comply with the FWA may constitute unethical behavior and endanger research subjects. Failure to comply can delay research and generate sanctions against an investigator, NMCP or the Navy. OHRP has the authority to suspend or remove an institution's FWA. Part of OHRP's FWA will require investigators to complete appropriate institutional training before conducting human subject research. Term #8 states: "The institution and designated IRBs have established (or will establish within 90 days), and will provide to OHRP upon request, education and oversight mechanisms (appropriate to the nature and volume of its research) to verify that research investigators, IRB members and staff, and other relevant personnel maintain continuing knowledge of, and comply with, relevant Federal regulations, OHRP guidance, other applicable guidance, State and local law, and institutional policies for the protection of human subjects. The institution and the designated IRBs will require documentation of such training from research investigators as a condition for conducting HHS-supported human subject research."

This booklet contains educational materials and federal regulations related to the principles and laws governing human subjects research. The National Institutes of Health (NIH) has prepared a web-based tutorial, "Human Participants Protections Education for Research Teams", that is intended to provide background information and basic concepts of protection of human research participants. This is a web-based tutorial for use by those involved in the design and conduct of research involving human subjects. The course is presented in 5 modules and covers key historical events and current issues in the protection of human research subjects, ethical principles federal regulations and guidelines, special populations, informed consent, the role of the Institutional Review Board, and responsibilities of researchers. There is a quiz at the end of each module. A log-in name and password are established at the outset so that you can return at a later time(s) to complete all 5 modules. After completion of all 5 modules, a certificate of completion is issued. **Print the certificate, sign, and forward or fax a copy to CIRD (Fax: 953-5298). Completion of the tutorial is a requirement for all principal, associate and sub-investigators of a human subjects protocol.**

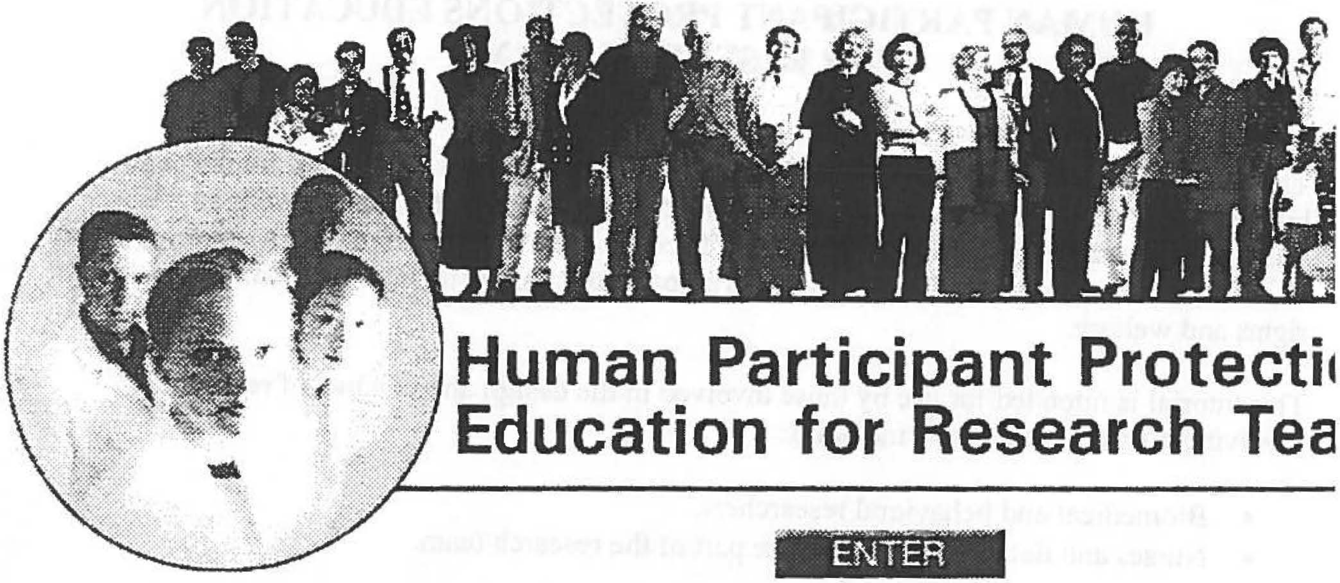
The web address is: http://cme.nci.nih.gov/

A copy of the tutorial is included in this booklet for your reference. Principal investigators are responsible for ensuring that newly added investigators to a study have completed the NIH tutorial if they have not previously done so. Also included is a glossary of terms related to human subjects research prepared by NIH.

The second section of this booklet includes local instructions for the consenting process. Proper consenting of subjects is an essential part of ethical research and care must be taken to ensure that a study, its risks and benefits are communicated to subjects not only in a written document, but verbally as well.

The remaining sections include federal guidelines and regulations regarding human subjects research. These include the Belmont Report (the "Common Rule"), Code of Federal Regulations 45 part 46, subparts A, B and D, and Code of Federal regulations 32 part 219, 10 USC 980 and a memo regarding its interpretation with respect to DoD research involving children. The latter statute places limitations of some types of human subjects research in DoD institutions.

Clinical Research Support
Clinical Investigation and Research Department
Phone: 953-5939
FAX: 953-5298



Human Participant Protecti
Education for Research Tea

ENTER

U.S. Department of Health and Human Services
National Institutes of Health

Returning users can click here to login.

HUMAN PARTICIPANT PROTECTIONS EDUCATION FOR RESEARCH TEAMS

The mission of the National Institutes of Health (NIH) is to improve human health through biomedical and behavioral research. Conducting research involving human participants is a necessary and important part of that mission. Therefore, the NIH is committed to assuring that all of its research activities involving human participants are conducted in a way that promotes their rights and welfare.

This tutorial is intended for use by those involved in the design and conduct of research involving human participants, including:

- Biomedical and behavioral researchers,
- Nurses and data managers who are part of the research team.

This tutorial presents common concepts, principles, and issues related to protection of human participants. The information presented is neither prescriptive nor exhaustive and is intended to act as a companion piece to your institutional policy, as well as local, state, and federal regulations applicable to human research. The tutorial will help you and your team identify research activities that involve human participants, and help you understand how to protect the rights and welfare of all human participants involved in research.

Learner Objectives

Upon completion of this course, the learner will be able to:

- Identify key historical events and current issues in research that impact guidelines and legislation on human participant protection in research.
- Identify the ethical principles that guide the conduct of research with human participants.
- Demonstrate the ability to use the guidelines and federal regulations to protect human participants throughout the research process.
- Describe guidelines for the protection of special populations in research.
- Define informed consent and the components necessary for a valid consent.
- Describe the role and responsibilities of the IRB in the protection of human participants.
- Recognize the roles, responsibilities, and interactions of federal agencies, institutions, and researchers in conducting research with human participants.

HISTORY

Nazi Medical War Crimes

Although not the first example of harmful research on unwilling human participants, the experiments conducted by the Nazi physicians during World War II were unprecedented in their scope and the degree of harm and suffering to which human beings were subjected. The "medical experiments" were performed on thousands of concentration camp prisoners and included such deadly studies as injecting people with gasoline and live viruses, immersion in ice water, and forcing people to ingest poisons.

In December 1946, 23 physicians and administrators, many of them leading members of the German medical hierarchy, were indicted before the war crimes tribunal at Nuremberg for their willing participation in the systematic torture, mutilation, and killing of the prisoners in experiments. Despite the arguments of the German physicians that the experiments were medically justified, the Nuremberg Military Tribunals condemned the experiments as "crimes against humanity"; 16 of the 23 physicians were found guilty and imprisoned, and 7 were sentenced to death. In the August 1947 verdict, the judges included a section called "Permissible Medical Experiments." This section became known as the Nuremberg Code and has formed the basis for ethics codes internationally.

The Tuskegee Syphilis Study

The most notorious example in the United States of prolonged and knowing violations of the rights of a vulnerable group of research participants was the long-term study of black males conducted at Tuskegee by the United States Public Health Service. This study was initiated in the 1930s as a study of the natural history of untreated syphilis and continued until 1972.

Over 400 black men with syphilis participated and about 200 men without syphilis served as controls. The men were recruited without informed consent and, in fact, were misinformed that some of the procedures done in the interests of research (e.g., spinal taps) were actually "special free treatment."

By 1936, it was apparent that many more infected men than controls had developed complications and, ten years later, a report of the study indicated that the death rate among those with syphilis was about twice as high as it was among the controls. In the 1940s, penicillin was found to be effective in the treatment of syphilis. The study continued, however, and the men were neither informed nor treated with the antibiotic.

The first accounts of this study appeared in the national press in 1972. The resulting public outrage led to the appointment of an ad hoc advisory panel by the Department of Health, Education and Welfare to review the study and give advice on how to assure that such experiments would never again be conducted. Among the recommendations was the request that Congress establish a "permanent body with the authority to regulate, at least, all federally-supported research involving human subjects."

In acknowledgement of its responsibility, the government continues to compensate the surviving participants and the families of deceased participants.

The Jewish Chronic Disease Hospital Study

In 1963, studies were undertaken at New York's Jewish Chronic Disease Hospital to understand whether the body's inability to reject cancer cells was due to cancer or debilitation. Previous studies had indicated that healthy persons reject cancer cells promptly and the researchers allegedly believed that the debilitated patients would also reject the cancers but at a substantially slower rate when compared to healthy participants.

These studies involved the injection of foreign, live cancer cells into patients who were hospitalized with various chronic debilitating diseases. The consent had been given orally, but did not include a discussion on the injection of cancer cells, and a consent was not documented. The researchers felt that documentation was unnecessary because it was customary to undertake much more dangerous medical procedures without the use of consent forms.

Further, patients were not told that they would receive cancer cells because the researchers felt it would unnecessarily frighten the patients. Researchers defended this view on the basis that they had good cause to predict that the cancer cells were going to be rejected.
In subsequent review proceedings conducted by the Board of Regents of the State University of New York, it was found that the study had not been presented to the hospital's research committee and that the several physicians responsible for the patients' care had not been consulted. The researchers were found guilty of fraud, deceit and unprofessional conduct.

The Willowbrook Study

The vulnerability of children, especially institutionalized children, as participants in research is demonstrated in a series of studies conducted from 1963 through 1966 at the Willowbrook State School, a New York institution for "mentally defective" children. In order to gain an understanding of the natural history of infectious hepatitis under controlled circumstances, newly-admitted children were deliberately infected with the hepatitis virus. Researchers defended the deliberate injection of these children by pointing out that the vast majority of them acquired the infection anyway while at Willowbrook, given the crowded and unsanitary conditions, and because only children whose parents had given consent were included.

During the course of these studies, Willowbrook closed its doors to new patients, claiming overcrowded conditions. However, the hepatitis program, because it occupied its own space at the institution, was able to continue to admit new patients. Thus, in some cases, parents found they were unable to admit their child to Willowbrook unless they agreed to his or her participation in the studies.

This controversial case raised important questions about the adequacy and freedom of consent, inadequate disclosure of the child's risk of later developing chronic liver disease, and the lack of information given to parents about access to doses of gamma-globulin for other children.

DEVELOPTMENT OF CODES OF RESEARCH ETHICS

The Nuremberg Code

The Nuremberg Code served as the first set of principles outlining professional ethics for medical researchers. The ten points included the statement that a "voluntary consent of the human subject is absolutely essential" and further established that animal experimentation should precede human experimentation; all unnecessary physical and mental suffering and injury should be avoided; the degree of risk to the participants should never exceed the "humanitarian importance of the problem" and should be minimized through "proper preparations"; and that the participants should always be at liberty to withdraw from the experiments. This set of points established the basic principles that must be observed in order to satisfy moral, ethical, and legal concepts in the conduct of human participant research. It has been the model for many professional and governmental codes since the 1950s, and has, in effect, served as the first international standard for the conduct of research.

Declaration of Helsinki

The Declaration of Helsinki is the code developed by the World Medical Association for the medical community in response to Nuremberg. The Declaration made an important distinction between therapeutic and non-therapeutic research and, like the Nuremberg Code, it made informed consent a central requirement for ethical research, but allowing for surrogate consent when the research participant is incompetent, physically or mentally incapable of giving consent, or a minor. However, the Declaration states that research with these groups should only be conducted when the research is necessary to promote the health of the population represented, and when this research cannot be performed on legally competent persons. It further states that when the subject is legally incompetent, but able to give assent to decisions about participation in research, then assent must be obtained in addition to the consent of the legally authorized representative.

The Declaration has been revised five times, most recently October 2000, and includes in its 32 principles the statement that "the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods." Although it says that this does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists, this stipulation is very controversial since some interpret it to mean that a placebo should never be used whenever effective therapy is available, regardless of the seriousness of the condition being studied. The Declaration is important in the history of research ethics as the first significant effort of the medical community to regulate itself.

Belmont Report

In the 1950's and 1960's, federal funding for biomedical research increased dramatically but at the same time there was increasing public concern expressed about research reports such as Tuskegee and other biomedical abuses.

In response to this public outcry, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 to make recommendations for the conduct of research involving humans. The primary task of the National Commission was to identify the ethical principles that would guide all research involving humans. In 1979, the National Commission wrote *The Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects* which is the cornerstone of ethical principles upon which the federal regulations for the protection of human research participants are based. By 1981, the Department of Health and Human Services and the Food and Drug Administration published regulations based on the Belmont Principles. Ten years later, in 1991, 17 federal departments and agencies agreed to adopt the basic human participant protections, generally referred to as the Common Rule (Title 45 Code of Federal Regulations Part 46).

GUIDING PRINCIPLES

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote their report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, commonly called the *Belmont Report*. In this report the Commission identified and described the basic ethical principles that underlie research. The Commission considered the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine in order to "know what activities ought to undergo review for the protection of human subjects of research". The report also describes the assessment of risk-benefit criteria in the determination of appropriateness of research on participants, appropriate guidelines for this assessment, and the nature and definition of informed consent. The three fundamental ethical principles that guide the ethical conduct of research involving human participants are:

1. **Respect for Persons**
2. **Beneficence**
3. **Justice**

Respect for Persons

The principle of respect for persons incorporates at least two ethical convictions.

1. Individuals should be treated as autonomous agents.

"An autonomous person is an individual capable of deliberation about personal goals and of acting under such deliberation. To respect autonomy is to give weight to the autonomous persons' considered opinions and choices while refraining from obstructing their actions..." (Belmont Report).

Prospective research participants must be given the information they need to determine whether or not to participate in a study. There should be no pressure to participate and ample time to decide. Respect for persons demands that participants enter into the research voluntarily and with adequate information, this is called informed consent.

2. Persons with diminished autonomy may need additional protections.

Special provision may need to be made when comprehension is severely limited or when a class of participants is considered incapable of informed decision-making (such as with children, people with severe developmental disorders or dementias). Even for these persons, however, respect requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research activities. In some cases, respect for persons may require seeking the permission of other parties, such as a parent or legal guardian. The judgment that one lacks autonomy should be periodically reevaluated and may vary in different situations.

Beneficence

Human participants are treated in an ethical manner not only by respecting their decision and protecting them from harm, but also by making efforts to secure their well-being. The principle of beneficence obligates the researcher to maximize possible benefits and minimize possible harm.

The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the involved harms or risks. Balancing risks and benefits is an important consideration. The goal of much research is societal benefit, however, in the interest of securing societal benefits; no individual shall be intentionally injured.

Justice

The ethical considerations of risks versus benefits leads to the question of justice. This principle requires that we treat participants fairly, and involves questions such as who should bear the risks of research, and who should receive its benefits?

Justice is a difficult and complex ethical issue. Attempts must be made at all times in the study to distribute the risks and benefits fairly and without bias. Also, unless there is clear justification, research should not involve persons from groups that are unlikely to benefit from subsequent applications of the research. The concept of justice may be questioned when deciding who will be given an opportunity to participate, who will be excluded, and the reason for exclusion. When making such decisions, the researcher must ask: Are some classes of persons being selected simply because of their availability, their compromised position, or their vulnerability - rather than for reasons directly related to the problem being studied?

CURRENT ISSUES

As you have learned in the previous section, it has been current events and issues in society, science, and research that have stimulated governments to regulate research activities to protect human participants. In the United States, federal regulations and policies have been developing since the 1960's and continue to expand as new fields of science and research create the demand for increased numbers of humans to participate in research studies. Today's rapidly developing fields of molecular biology and information technology have heightened public concerns and fostered public debate of a number of complex public issues related to human participant protection. Major issues include:

- **Privacy and Confidentiality**
- **Public Awareness of Research**
- **Human Genome Research**

Privacy and Confidentiality

Rapid advances in the acquisition, storage, analysis, and communication of data by electronic means, combined with the recent advances in biomedical research, have posed challenges for the clinical research community. One of these challenges is in the maintenance of confidentiality of personally identifiable health information. The goal of the research community, and of society generally, should be to continue to protect the confidentiality of research information without compromising the critical research necessary to improve human health.

Patient and Public Awareness of Research

In general, the public is more aware of research due to the increased use of the Internet and the national news offering frequent information about research results on new drugs and medical technologies. Both the proliferation of media attention along with increased public awareness of biomedical research heightens the importance of the research community's continued commitment to protecting the rights of human participants, thus, maintaining the public trust.

Human Genome Research

Human genome research is beginning to provide researchers information regarding the genetic make-up of individuals, especially the potential of a person to develop a certain disease. However, the relationship between having a certain gene and developing a disease is very complex and influenced by many factors. Additionally, the mapping of the details of the human genome provides the template for understanding the role of specific genes in disease. The complicated task now ahead is translating this information into knowledge.

Researchers are still years away from fully understanding the relationship of risk of disease development to genetic make-up for many diseases and probably decades away from having interventions to prevent disease that may be based on genetic risk or molecular therapies. Ethical issues can arise concerning the participant's right or need to know research data, especially genetic data, if the future health implication of such information is not well understood. The researcher's understanding of regulations regarding informed consent are critical in helping the scientist understand their responsibilities and protecting human rights of research participants.

THE BASICS

This chapter defines the basic terms used in the federal guidelines and regulations protecting participants in research. Understanding who is the research participant and when a research study includes human participants guides the researcher and team in applying the appropriate policies. The roles and responsibilities of the researcher and the team in relation to human participant protections are explored.

Who, When, Why?

Research is a systematic investigation (including development, testing and evaluation) designed to discover or contribute to a body of generalizable knowledge. Not all research involves human participants, but when they are involved researchers and their teams are legally and ethically obligated to protect human participants.

WHO is the research participant?

The human participant is a living individual about whom a researcher obtains either (1) data through intervention or interaction with the individual, or (2) identifiable private information.

WHEN does research require the inclusion of human participant protections?

Since data is collected directly or indirectly by the researcher, protection of participants extends to a wide range of research, including that which involves tissue specimens, medical records, genetic material, behavioral and/or biomedical assessments, and treatments. Legal obligations to protect human participants apply, for example, to the research that uses:

- Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, even if you did not collect these materials;
- Residual diagnostic specimens, including specimens obtained for routine patient care that would have been discarded if not used for research;
- Private information, such as medical information, that can be readily identified with individuals, even if the information was not specifically collected for the study in question. Research on cell lines or DNA samples that can be associated with individuals falls into this category.

Each researcher must decide if the study includes human participants and, if so, become familiar with the regulations governing the rights and safety of the research participants.

The decision is governed by:

- The researcher's institutional rules,
- The requirements of the researcher's Institutional Review Board (IRB),
- Regulations in the Code of Federal Regulations, Title 45, Part 46: Protection of Human Subjects and Food and Drug Administration Regulations 21CFR, Part 50, 56.

To help you make this important decision you may want to review the Human Subjects Regulations Decision Charts and Research on Human Specimens.

WHY is it important to protect human research participants?

Conducting research involving humans is a necessary and crucial step to improving human health through biomedical and behavioral research. In this era of rapidly advancing medical technology, increasing complexity and pace of research, revolutionary genetic research, and ever-increasing threats to personal privacy, the protection of human participants is a priority. Researchers and the research team have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities.

Emphasis on enhancing protection is needed to:

- promote the safety and well being of human participants in research,
- adhere to the ethical values and principles underlying research,
- implement ethical and scientifically valid research, and
- allay concerns by the general public about the responsible conduct of research.

The responsibility to protect participants volunteering in research belongs to a variety of individuals, groups, and organizations.

- Federal agencies such as the National Institutes of Health and the Food and Drug Administration (FDA) provide policies and guidelines concerning participant protections for clinical trials research.
- Funding agencies/sponsors are responsible by ensuring that grantees adhere to the federal regulations.
- Scientific peer review groups, institutional review boards and data and safety monitoring boards review research and oversee human participant protections at different stages in the research process.

The researcher conducting the study has the primary responsibility to ensure that participants in research are fully informed of their rights, and properly protected.

The researcher is specifically responsible for assuring that:

- The study is properly designed, scientifically sound and yields valid results;
- Participants meet selection and eligibility requirements;
- The study is approved by the IRB and conducted according to the protocol;
- The informed consent is appropriately obtained;
- Protocol changes and adverse events are reported to the appropriate boards and authorities;
- The rights and welfare of participants is monitored throughout the trial; and
- All members of the research team are qualified, trained in research methods and human participant protections.

Research team members (key personnel) whose responsibilities are delegated by the researcher also have a role in ensuring integrity of the study by consistently applying procedures and assuring that the rights of participants are safeguarded.
Research team members are typically responsible for:

- Day-to-day protocol decision-making related to the study conduct;
- Participant recruitment, selection and eligibility;
- Clarification of the complexities of the protocol to the participant and others;
- Collecting participant information and entering data using procedures to maintain privacy and confidentiality; and
- Ensuring that the rights and welfare of participants are monitored throughout the study.

PARTICIPANT SELECTION

In selecting participants for research, researchers are responsible to ensure that selection is equitable. No individual or group should be overburdened without the acquisition of potential benefits. This is based on the principle of justice. The researcher must consider:

- the population from which the sample is drawn,
- the feasibility of acquiring the number of participants needed, and
- the recruitment procedures to ensure an equitable distribution across the population.

Inclusion and exclusion criteria are developed in the planning and written into the protocol. These should take into account the 1994 NIH Guidelines for Inclusion of Women and Minorities in Research and any vulnerable populations.

The guidelines issued by NIH for the inclusion of women and minorities as participants in research require the inclusion of women and minority populations "so that the research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study." If a proposed study includes a population in which women and minorities are not appropriately represented, the researcher must provide "a clear compelling rationale for their exclusion or inadequate representation."

The researcher must consider other issues with the potential to affect selection of participants. Patients may also be susceptible to real or imaginary pressure to participate. If a researcher also serves as a patient's primary physician, the patient may feel obliged to participate in the research out of a desire to please in gratitude, or out of fear that failure to do so will result in hostility or abandonment. Patients who are dependent upon a particular facility for their care (e.g., Veterans Hospitals, Indian Health Service Hospitals, or community health clinics) may feel that they will be treated less well or with less favor if they refuse to participate in research.

VULNERABLE POPULATIONS

Vulnerable research participants are persons who are relatively or absolutely incapable of protecting their own interests. The researcher and the research team should be cognizant of the special problems of research involving vulnerable populations, justify the proposed involvement of these populations in the research, and include additional safeguards for their safety and welfare. These populations include:

- Children,
- Individuals with questionable capacity to consent,
- Prisoners,
- Fetuses and pregnant women,
- Terminally ill,
- Students/employees,
- Comatose patients.

Brief information about the regulation on research with children, individuals with questionable capacity to consent and prisoners are presented, but the researcher and the team should be familiar with all of the policies by linking to the suggested sites on the next page and in the resources list at the end of the program.

The regulation pertaining to children as research participants is found in 45 CFR 46.Subpart D. Risk/benefit categories found in this regulation include those:

- not involving greater than minimal risk;
- involving greater than minimal risk but presenting the prospect of direct benefit to the child;
- involving greater than minimal risk and no prospect of direct benefit to the child, but likely to yield knowledge about the child's disease; and
- studies not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem for children.

In 1998, the NIH wrote a policy and guidelines for the inclusion of children as research participants in all studies supported and/or conducted by the NIH. The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults that may also affect children. Proposals for research involving human participants must include a description of plans for including children or an explanation for their exclusion in the research. This policy is found at http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Legally, children have not attained an age where they can consent to research or treatment. Therefore, the parent or guardian may provide "permission" for the child to participate in a study. In most cases, the child must indicate his willingness to participate by assenting to the study. For further information link to: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Research involving individuals with questionable capacity to consent requires careful consideration in order to provide these participants with additional safeguards. This vulnerable population may include persons with psychiatric illness, neurologic conditions, substance use and various metabolic disorders. Some individuals may not be able to give informed consent, so "permission" for certain kinds of research can be given by a legally authorized representative and "assent" of the participant is substituted.

Prisoners are confined under the strict control of people whom they must please and to whom they must appear cooperative if they are to earn their release. These potential participants may believe, probably as a result of their dependent situation, that agreeing to participate in research will be viewed positively by their wardens. These individuals are also readily available in large numbers. In the past, prisoners have accepted the risks of research in disproportionate numbers, while the benefits of the research in which they participated went to all segments of the population. Therefore, special regulations are in place that restrict the involvement of prisoners in research.

With these caveats in mind and an understanding of the federal regulations, researchers must also be careful not to *overprotect* vulnerable populations so that they are excluded from participating in research in which they wish to participate, particularly where the research involves therapies for conditions with no available treatments. So, too, patients with serious or poorly understood disorders may want to participate frequently in research designed to provide a better understanding of their condition. The fact that the participants may be either a patient of the principal researcher or a patient in the clinic or hospital where the researcher conducts the study should not preclude them from the opportunity to choose to participate as often as they wish.

PROTECTION OF PRIVACY AND CONFIDENTIALITY

Privacy is defined in terms of having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. When participants in research give information about themselves to the research team or institution, they do so in a relationship of trust. They expect that the information will be shared only as necessary. The research team must respect the participant's trust and not betray the confidence placed in them.

Confidentiality pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged without permission to others in ways that are inconsistent with the understanding of the original disclosure. Researchers ordinarily use information that participants have disclosed or provided voluntarily (i.e., with their informed consent) for research purposes. Under these circumstances, there is little reason for concern about privacy, other than to assure that appropriate confidentiality of research data is maintained. In most research, assuring confidentiality can occur by following routine practices:

- substitute codes for identifiers or encrypt identifiable data,
- remove face sheets (containing identifiers such as names and addresses) from survey instruments containing data,
- properly dispose of computer sheets and other papers,
- limit access to identifiable data,
- educate the research staff on the importance of confidentiality,
- store paper research records in locked cabinets or provide security codes for computerized records.

In studies of participants with sensitive, stigmatizing or illegal personal information (e.g., persons who have sexually abused children, tested positive for HIV, or who have sought treatment in a drug abuse program), keeping the identity of participants confidential may be as or more important than keeping the data obtained about the participants confidential. In such cases, any written record linking participants to the study can create a threat to confidentiality. Having the participants in these studies sign consent forms may increase the risk of a breach of confidentiality, because the consent form itself constitutes a record, complete with signature, that identifies particular individuals. The federal policy allows the IRB to waive the requirement for the researcher to obtain a signed consent form in cases where it will be the only record linking participants to the research, and where a breach of confidentiality presents the principal risk of harm that might result from the research.

When data are being collected about sensitive issues (e.g., illegal behavior, alcohol or drug use, sexual practices or preferences), protection of confidentiality consists of more than preventing accidental disclosures. There have been instances where the identities of participants or research data about particular participants have been sought by law enforcement agencies, sometimes under subpoena, and with the threat of incarceration of the uncooperative researcher. Under federal law, and some state laws, researchers can obtain an advance Certificate of Confidentiality that will provide protection even against a subpoena for research data.

CASE STUDY

The following case study illustrates the definitions used to determine if specimens are considered human participant research and the possible exemption from IRB review.

A highly respected researcher at Outstanding University in Montana is conducting studies on markers of cancer progression. Dr. Respected is ready to initiate a new set of experiments using tissue specimens from patients with early stage breast cancer. To carry out these studies requires access to archival breast cancer specimens that are not available from the local pathologist. Since she will not have sufficient specimens, Dr. Respected makes arrangements with a researcher in Minneapolis to send additional specimens. These arrive with a code that leaves Dr. Respected without any information about who the patients are. Many of the patients are still living and outcome information may be required later. However, since outcome information may be required later, Dr. Green retains a key to the patients' identity in his laboratory in Minneapolis. Some of the specimens were collected from other researchers in the Midwest and placed in Dr. Green's bank.

Q: Is Dr. Respected working with human participants?
A: Yes, because they are using tissue specimens from living individuals.

Q: Are these patients identified?
A: Yes, since the provider can relate the code to patient identity.

Q: Is the study exempt from the common rule (45CFR46)?
A: No, since the specimens can be identified.

INFORMED CONSENT

Once the researcher has a carefully defined research question, a valid design and protocol for a research project, it is time to plan for the informed consent for those invited to participate. Planning involves deciding:

- what information to provide to potential participants, both in writing and in discussions;
- deciding who is going to present the information and at what point in your interactions with participants;
- how the participants understanding will be assessed; and
- who will obtain the participant's signature or agreement.

This plan must be reviewed and approved by an IRB before approaching potential participants.

Background

Informed consent, as a legal, regulatory, and ethical concept, has become widely accepted as an integral part of research. Current requirements for informed consent owe much to the legal system, but the underlying values are deeply embedded in American culture and the American character. Fundamentally, informed consent is based on respect for the individual, and in particular the individual's autonomy or capacity and right to define his or her own goals and make choices designed to achieve those goals for his/her own life. This right is well established in American jurisprudence and medical practice and applies to all types of medical interventions and clinical research. In clinical research, informed consent is the process of providing all relevant information about the purpose, risks, benefits, alternatives, and procedures to a potential participant, who consistent with his/her own interests and circumstances makes an informed decision about whether or not to participate. General requirements for informed consent are spelled out in the Common Rule at 45CFR.46.116.

Preparing the consent document for IRB review

The first step to take in the process of informed consent is preparing the written consent document for presentation to the IRB. This document should include all the elements listed in Table 1 (and required by 45CFR.46.116), as well as any other information you think prospective participants might need to make an informed decision about participation. Consent documents should be written in non-technical language that can be understood by the proposed participant population, consistent with their educational level, familiarity with research, and cultural views.

The consent document must make clear that participation in research is voluntary, and should not include any language waiving or appearing to waive participant's rights. In some cases, the researcher may want to request the IRB to approve a modification or waiver of the elements of informed consent as spelled out in the regulations.

Advertisements, fliers, or brochures that are prepared to recruit and inform potential participants about a study are considered part of the informed consent process and also require review and approval by the IRB.

Approaching research participants

Researchers and members of the research team are responsible for making sure that the process of informed consent conforms to the value of respecting individuals' right to make informed and voluntary decisions about research participation, as well as to the regulations guiding research with human participants. In this regard, after receiving approval for the consent plan from the IRB, there are several essential steps to take in the process of informed consent. The researcher and responsible research team members should:

- feel confident that the potential participant has the capacity to understand information, make decisions, and provide informed consent for the particular study;
- provide both written (as described above) and verbal information about the details of the study in a way that is understandable to the participant;
- be satisfied that the participant understands the information provided, has had an opportunity to ask questions, and an opportunity to deliberate about participation;
- be satisfied that the participant is in a position to make a voluntary decision, not coerced or unduly influenced by circumstances or other people;
- be satisfied that the participant affirmatively agrees to participate, as indicated in most cases by signing an informed consent document.

How does the researcher determine if a participant has the capacity to consent?

Adults who have sufficient mental capacity to understand the information provided, to appreciate how it is relevant to their circumstances, and to make a reasoned decision about whether or not to participate in a particular study, have the capacity to consent. Children (in most jurisdictions those under 18 years of age) do not have the legal capacity to provide their own consent.

Capacity can be affected by several things, including age, cognitive impairment, illness, and treatments. Capacity to consent for a study is study specific. For example, a person may have sufficient capacity to carry out their daily activities and make their own decisions, but not sufficient capacity to appreciate how the particulars of a given protocol might be relevant to them.

For some participants or groups of participants, you or the IRB may decide that an independent capacity assessment is a good idea. This may involve consulting with a psychiatrist or neurologist to make a determination about an individual's cognitive ability, and should include an independent assessment of the person's ability to understand the details and implications of the protocol being presented to them.

If a person is unable to provide his/her own consent, in some cases, a legally authorized representative can give permission for participation in research. A legally authorized representative is a legal guardian, a parent (for children only), and in some cases a validly designated durable power of attorney for health care (the latter is an evolving area). The researcher should check with institutional policies or assurance and the IRB.

What should the researcher think about when providing information to potential participants about the study?

The provision of information about a study usually involves more than just providing the written consent document for the potential participant to read. Verbal presentation of information and the opportunity to discuss and answer questions and concerns are an important part of the process, usually in addition to giving the person time to read the written consent form. Educational materials about the study or clinical research in general are helpful. If the researcher delegates the function of verbal presentation and discussion of a study to members of the team, the researcher must be sure they have sufficient knowledge of the protocol to answer questions appropriately. Delegation may have to be approved by the institution IRB.

How does the researcher assess the participant's understanding?

The researcher should feel satisfied that after the detailed information has been presented and discussed, the potential participant understands it well enough to make a decision. Of course, some studies are more complicated and involved than others. Researchers use many different strategies for determining whether or not a research participant understands. Sometimes it is clear at the end of a discussion, other times having a participant answer questions about the study either informally or even in writing may be appropriate. The best method may depend both on the complexity and risk level of the study as well as the potential participants. For some studies, time to deliberate or discuss the study with family, trusted friends or other health care providers can be very important.

How does the researcher know whether or not the participant's decision is voluntary?

Individuals who feel 'coerced' into making a decision about research participation or are in a position where it is impossible or extremely difficult for them to say no should not be enrolled into research. Coercion occurs if there is some threat of harm or punishment for refusal to participate. Individuals in relationships of unequal power or dependence have historically been particularly vulnerable to coercion. Examples might include telling a student he/she would fail a course, an employee that he/she would not be promoted, or a soldier that he/she would be reprimanded if they refused to participate in research. Coercion in research is rare due to the vigilance of research teams and IRBs.

All decisions, including a decision about research participation, are subject to the influences of one's previous experiences and circumstances. Sometimes understanding the reasons an individual is considering participation is helpful in assessing how voluntary a decision is. The goal is to be sure that individuals understand research participation as a choice or an option among other, albeit in some cases limited, options. Being sure that individuals understand that they can freely refuse to participate and/or withdraw at any time without penalty is critical to assuring voluntary consent.

Must the researcher always obtain an individual's written signature?

In most cases, consent to research participation is documented by obtaining the signature of the participant or the legally authorized representative on the written informed consent document. A copy of this document should be given to the person signing the form. By federal regulation, a signature is required on the written document that contains all the required elements of information, or on a short form and written summary of the information when the information has been presented orally, as spelled out in 45CFR.46.117(b)(2).

In some cases, a signed consent document is inappropriate. According to the federal regulations at 45CFR.46.117(c), the **IRB may waive** this requirement if it determines:

1. that there is a confidentiality risk and the only link between the participant and the research would be the consent document, **or**

2. that the research presents no more than minimal risk of harm and involves no procedures which normally require informed consent outside of research.

Case Study

A young man (23yo) comes to the medical center for possible participation in a novel high-dose chemotherapy study for a refractory tumor. He has been provided with the written consent document that contains all of the informational elements as required by the federal regulations and approved by the IRB. He states that he has read the consent form and has no questions. Prior to obtaining his signature, the researcher discusses the study with him and offers to answer any questions. In the course of this discussion, the researcher becomes concerned about how much of the study the young man actually understands. The researcher knows that the young man only has a 7th grade education, and is somewhat shy and non-communicative.

The nurse begins to ask him questions about the study to assess his understanding. He can tell the nurse that he will be admitted to the hospital to receive a strong new drug that might make him very sick while he is in the hospital, but that might also help his cancer. He also explains that he thinks the only other choice available to him is amputation of his arm. Upon further questioning, he says that he understands the study is trying to find out if this drug works in him and other people like him, and that there is no guarantee that it will help him.

However, he cannot provide the name or dose of the drug, describe how it will be given or how it is believed to work. He can remember a couple of the possible side effects, but not the majority of them (there is a long description of risks, about 3 pages, in the consent document). He cannot describe parts of the study that are purely for research, such as additional scans or the storage of tissue for analysis of tumor characteristics and future studies.

In your judgment, is he ready to sign the consent document? Are there other things that might be helpful before you proceed with asking him to sign the consent document?

Things that might be helpful before asking him to sign the consent document:

- Perhaps giving him additional time to deliberate and discuss with other members of the research team, or members of his family would be helpful;

- Perhaps consulting with another resource to evaluate either his capacity to give consent or his understanding of this particular study or both (maybe a psychiatrist, an ethics consultant, a social worker, or a small interdisciplinary group);

- Perhaps a group discussion among the research team regarding the adequacy of his understanding of the study;

- Explaining the study specifics again, especially the areas that are crucial to his understanding and his participation;

- If it were expected that other possible participants in this study might also have difficulty understanding the details of the study, perhaps developing pictures, a video, or some other visual explanation of the study would be helpful.

IRB REVIEW

In response to revelations of the Tuskegee Syphilis Study (1932-1972), The Department of Health and Human Services (DHHS) appointed a panel to review the study as well as the Department's policies and procedures for the protection of human participants in general. The panel concluded that Congress establish "a permanent board with the authority to regulate at least all federally supported research involving human subjects." In 1974, Congress passed the National Research Act which requires the establishment of Institutional Review Boards (IRBs) to review all DHHS funded research. The Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research which issued the Belmont Report, the seminal document that provides the ethical principles upon which we base our protections of research participants.

Also in 1974, DHHS established regulations for the Protection of Human Subjects of Biomedical and Behavioral Research that included IRB review procedures (45 Code of Federal Regulations (CFR) 46, Subpart A). These procedures were revised in 1981 in response to recommendations of the National Commission that delineated more carefully the IRB requirements, responsibilities, and procedures that IRBs were required to follow.

In 1991, to provide unity in the human protections system, the core DHHS regulations (Subpart A) were formally adopted by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human participant research. Subpart A subsequently became known as The Common Rule. Research to which DHHS regulations apply that involves fetuses or pregnant women, prisoners, or children is governed by special provisions (45CFR46 Subpart B, Subpart C and Subpart D, respectively).

The Food and Drug Administration (FDA) has its own regulations and policies concerning IRB review and are included in 21CFR56. The basic requirements for IRBs and for Informed Consent are congruent between the two sets of regulations.

Roles and Responsibilities of the IRB

An IRB protects the rights, safety, and welfare of human research participants by:

- reviewing research plans to ensure that in its judgement the research meets the criteria found at 45CFR46.111;
- confirming that the research plans do not expose participants to unreasonable risks;
- conducting continuing review of approved research at intervals commensurate with the degree of risk of the trial, but not less than once a year, to assure that human participant protections remain in force; and
- assessing suspected or alleged protocol violations, complaints raised by research participants, or violations of institutional policies.

The IRB has the authority to:

- approve, disapprove, or terminate all research activities that fall within its local jurisdiction according to relevant federal regulations and local institutional policy;
- require modifications in protocols, including previously approved research;
- require that information, in addition to that specifically mentioned in 45CFR46.116, be given to participants when the IRB deems that this information would add to the protection of their rights and welfare;
- require documentation of informed consent or allow waiver of documentation, in accordance with 45CFR46.117.

For more information on the roles and responsibilities of the IRB, see 45CFR46.109.

IRB Membership

IRBs are comprised of sufficiently qualified men and women who have no vested interest in the research study or its outcomes. Their responsibility is to assure that all research studies are ethical and justified.

Federal regulations mandate that an IRB must have at least five members with varied backgrounds, although it may have as many members as necessary to perform a complete and adequate review of research activities. Membership should be diverse regarding race, gender, cultural heritage, and sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of research participants.

If an IRB reviews research that involves vulnerable populations, such as children, prisoners, pregnant women, disabled, or cognitively impaired persons, the IRB should include one or more persons who are knowledgeable about and experienced in working with these populations.

No IRB may consist entirely of members of one profession; each IRB should include at least one member whose primary concerns are in scientific areas and one member whose primary concerns are in nonscientific areas. Each IRB should include at least one member not affiliated with the institution. No IRB may have a member participate in the IRB's review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

The IRB may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that of the IRB members. These individuals are not voting members.

Criteria for IRB Approval of Research

In order to approve research, the IRB must assure that the following requirements are satisfied:

1. Risks to participants are minimized by using procedures that are consistent with sound research design and which do not unnecessarily expose participants to risk;

2. Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those that may result from the research, as distinguished from those that participants would receive if not participating in the research;

3. Selection of participants is equitable. The IRB should consider the purposes of the research and the setting in which the research will be conducted and should be particularly mindful of the special problems of research involving vulnerable populations. Participants should share equally in foreseeable benefits and risks.

4. Informed consent is sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by 45CFR46.116;

5. Informed consent is appropriately documented, in accordance with, and to the extent required by 45CFR46.117;

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants;

7. When appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data; and,

8. Additionally, when some or all of the participants are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, mentally disabled, economically or educationally disadvantaged persons) additional safeguards are included in the study to protect the rights and welfare of these participants.

Assessment of Risks and Benefits

When approving research, the IRB must assess whether the anticipated benefit of the research, either of new knowledge or of improved health for the research participants, justifies inviting anyone to undertake the risks. The IRB should disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

Risks to individuals are classified as physical, psychological, social, and economic. In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies participants would undergo even if not engaged in research, should be considered.

Once risks have been identified, the IRB must assess whether the research poses minimal or greater than minimal risk. Minimal risk (defined in 45CFR46.102) is defined as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The concept of minimal risk is used in the federal policy for three purposes. First, the concept guides the IRB to determine if the proposed research should get full board review or can be expedited. Second, it is used to determine what research can proceed without consent and, third, the concept is used to decide when documentation (a consent form) should be used.

IRBs must ensure that risks to participants are minimized. Researchers should include strategies for reducing risks in the protocol. For example:

- Precautions, safeguards, and alternatives should be incorporated into the protocol to reduce the probability of harm or to limit its severity or duration.
- IRBs should determine whether the researchers are competent in the planned area and whether they serve dual roles (e.g., as clinician and researcher) that may cause conflicts of interest and lead to a "therapeutic misconception" held by the research participant.
- IRBs should assess whether the research design will yield useful data so that research participants are not exposed to risks without sufficient justification.

The IRB must be notified of any unanticipated problem involving risks to participants or others, including physical or psychological injury to participants, improper disclosure of private information, economic loss, or other potentially harmful occurrences.

Depending on the level of risk of the research protocol and the participant population, IRBs can ask for full board review or expedited review.

Expedited review: For certain kinds of research involving no more than minimal risk and for minor changes in approved research, the IRB chair or a designated voting member or group of voting members review the proposed research rather than the entire IRB. It cannot be assumed that research poses minimal risk just because it involves only interview or survey data collection. Sensitive questions may be included leading to distress that exposes participants to greater than minimal risk. Loss of confidentiality can cause harm to participants, their relatives, and to others.

When **full board review** is necessary, the research proposal is presented and discussed at a convened meeting at which a quorum of IRB members is present. For the research to be approved, it must receive the approval of a majority of those voting members present.

Research exemptions from IRB review

Certain low-risk research is exempt from the requirements in the federal regulations concerning IRB review and approval. If a study falls into one of the exempt categories, researchers still have ethical responsibilities to protect participants' rights. The researcher should not make the final determination of exemption from the applicable federal regulations or the provisions of their institution. Check with your institution's guidelines or IRB policies to determine who will make the determination of exemption for a proposed study.

The following are the six exempt categories as listed in 45CFR46.101(b):

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

   a. information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and
   b. any disclosure of the human participant's responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participant's financial standing, employability or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) of this section, if:

   c. the participants are elected or appointed public officials or candidates for public office; or
   d. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available or if the information is recorded by the researcher in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.

5. Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine public health benefit or service programs.

6. Taste and food quality evaluation and consumer acceptance studies.

These exemptions do not apply to research involving prisoners, fetuses, pregnant women or human in vitro fertilization. Further, the exemption in item two (above), does not apply to children, except for research involving observations of public behavior when the researcher(s) do not participate in the activities being observed.

ONGOING PROTECTIONS

The researcher and the team's obligation to protect human research participants does not end with initial approval of the study or a signed informed consent document. In clinical research, the commitment to participants is to safeguard their interests throughout the study.

These commitments (for example, appropriate clinical monitoring, management of adverse events, and treatment of injuries) are written into the informed consent document. An ongoing challenge is the need to reassess the balance between risks and benefits, both to the participant and, in some genetic research, to the participant's family, as new information becomes available.

Ongoing informed consent

Informed consent is a continuous communication process that spans the entire study. Many of the elements of informed consent that have been previously discussed apply throughout the study. The researcher and the research team should:

- Feel confident that the participant maintains the ability to understand information, make an informed decision, and voluntarily continues to participate;
- Provide written and verbal information about emerging study details in a manner understandable to the participant; and
- Be satisfied that the participant understands the information provided, has had an opportunity to discuss the information and ask questions, and understands that he/she may withdraw from the study at any time.

When changes in the study occur and/or significant new findings have developed during the course of the study that may affect the participant and his/her willingness to continue participation, additional informed consent may be necessary. A re-consent may involve the signing of a new informed consent. Consult your IRB for the requirements for study changes and re-consent processes.

Adverse event reporting

The Common Rule (45CFR46, Subpart A) defines an adverse event as "unanticipated problems" involving risks to study participants or others. The regulations require written procedures and policies for ensuring reporting of the adverse event.

The researcher and the team have responsibility to report any adverse events to the IRB, the study sponsor, the FDA (if an investigational agent or device is involved in the study and the researcher is the Investigational New Drug (IND) sponsor) and the NIH. The researcher and the team should be familiar with the local IRB policies, adhere to these policies and maintain a copy of these policies in the research study file. The researcher is also responsible for accurate documentation, investigation, and follow-up of all possible study-related adverse events.

For further guidance in reporting adverse events to the IRB for NIH supported multi-center clinical trials, see http://grants.nih.gov/grants/guide/notice-files/not99-107.html.

The data and safety monitoring plans required for all federally funded research studies must include a description of the reporting mechanism should an adverse event occur. Generally, the NIH Institute or Center funding and/or sponsoring the IND for the agent establishes operational definitions of adverse events that can be applied to their sponsored studies and specific reporting mechanisms. For example, The National Cancer Institute defines adverse drug reactions in its clinical trials involving antineoplastic agents as:

- previously unknown toxicities, and
- life-threatening or fatal toxicities regardless of whether or not previously known. See http://ctep.info.nih.gov/AdEERS/default.htm for more information.

If the study includes an investigational agent or medical device, the research team must adhere to both the sponsor (NIH Institute or Center) and the FDA policies for adverse event reporting.

The FDA, in Federal Regulations 21 CFR Part 312, defines adverse events as any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment. In the guideline entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", the Agency further clarifies and defines serious adverse events stemming from a study involving an investigational agent as any untoward medical condition that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity or a congenital anomaly/birth defects. The FDA also has specific reporting procedures.

Continuous data and safety monitoring

Data and safety monitoring plays an essential role in protecting the safety of participants and assuring integrity of the research study.

The objective of data and safety monitoring is to:

- assure that risks associated with research participation are minimized to the extent practical and possible;
- avoid exposure of participants to excessive risk;
- ensure data integrity; and
- stop a study if safety concerns arise or as soon as its objectives have been met.

The monitoring should be commensurate with risks and with the size and complexity of the research. The NIH requires data and safety monitoring in the form of Data and Safety Monitoring Board (DSMB) for all Phase III clinical trials (large, usually multi-center, randomized studies). A DSMB may also be appropriate and necessary for Phase I and Phase II clinical trials if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.

The DSMB is an independent committee whose members include, at a minimum, a statistician and a clinical expert in the area being studied. Other members include experts in all scientific disciplines needed to interpret the data and ensure participant safety. They may also include clinical trial experts, statisticians, bioethicists, and other clinicians knowledgeable about the research study subject matter.

DSMB members protect the safety of participants by being familiar with the study, proposing appropriate analysis, and periodically reviewing the developing outcome and safety data. The DSMB assures the integrity of the study by reviewing data on such aspects as participant enrollment, site visits, study procedures, forms completion, data quality, losses to follow-up, and other measures of adherence to protocol. The DSMB monitors adverse events, discusses concerns in this regard, and makes recommendations regarding appropriate study and operational changes. The DSMB monitoring function is above and beyond the oversight traditionally provided by the IRB and as such is particularly important for multicenter research studies.

For those Phase I and Phase II trials where the establishment of a DSMB is not required, researchers must submit a general description of the data and safety monitoring in a written plan. This data and safety monitoring plan is developed by the researcher and is trial specific. It must be included as part of the protocol and submitted to the local IRB. It is also reviewed and approved by the Institute or Center funding and/or sponsoring the IND for the agent before the trial begins.

All data and safety monitoring plans must include, at a minimum, a description of the reporting mechanism of adverse events to the IRB, appropriate institutional officials, FDA (if the researcher sponsors the IND for the agent), and NIH. Other issues that may be addressed include enrollment, retention, adherence, data completeness, safety, and efficacy. Researchers must ensure that the NIH is informed of actions, if any, taken by the IRB as a result of data and safety monitoring reviews.

NIH policy and guidance for data and safety monitoring can be found at:

- http://grants.nih.gov/grants/guide/notice-files/not98-084.html

Key points to remember about data and safety monitoring:

- Data and safety monitoring must occur periodically throughout each study.
- Periodic data summary reports are developed to determine if the study should change in any way or stop. Any resulting significant changes are implemented with the approval of the local IRB and are reported to appropriate institutional officials, the FDA (if the researcher sponsors the IND for the agent) and NIH.
- Careful adverse event reporting is timely. Safety problems must be identified and reported to the IRB, appropriate institutional officials, the FDA (if the researcher sponsors the IND for the agent) and the NIH in a manner as outlined in the protocol.

- The risk/benefit ratio must be reassessed based on any new internal or external data and information.

Continuing IRB Review of Ongoing Studies

At least annual review of the study by the IRB allows them to determine if there are any study related events that endanger the participants currently involved in the study or those who have completed the study. If there are, the IRB may require notification of participants, change to the informed consent or cessation of the study with notification to all participants. The IRB should receive adverse event reports from researchers to review, in lieu of receiving individual adverse event reports from each clinical site in a multi-site study. With a DSMB in place, the IRB can review written summary reports from the researcher after the DSMB review.

Case Study

This study is a NIH sponsored (sponsoring the IND for the investigational agent), phase III, multi-site clinical trial comparing a 4-drug combination of anti-retroviral drugs to a 3-drug combination. The objective is to ascertain whether, on the average, the new 4-drug combination can delay virologic progression of disease in HIV-infected persons. The 4-drug combination consists of the 3-drug combination plus an investigational drug, so the trial is a test of whether the new drug adds benefit. The trial will require the enrollment of several hundred volunteers, which is expected to take as long as two years. Treatment for each participant will continue using the initially assigned drug combination until there is clear evidence that the participant is not benefiting. The safety profile of the 3-drug combination is fairly well established from past studies, as is the safety profile for the new drug when it is given by itself to less ill persons than those who will enroll in the study. Very little is known about the ways the new drug might interact with the older combination to produce different kinds of problems.

Based on this case, consider the following scenarios:

- A few months after starting, there have been reports of very pronounced anemia in five different participants taking the new drug, and none in participants taking just the three-drug combination.

  Q: To whom should you report these results?
  A: The researcher must follow the data safety and monitoring plan as written in the protocol. According to federal policy for adverse events, these findings should be reported to the DSMB, IRB, NIH (appropriate Institute or Center) and the FDA only if the researcher sponsors the IND for the agent. The other sites will need to be notified as required in the protocol and according to the IRB policies.
- (Assuming the study continues) Later, but still before the study recruitment finishes, a summary of study results reveals that participants in the 4-drug group have better outcomes than expected and the observed difference is statistically significant.

Q: What might happen to your study?
A: The DSMB has the responsibility to review interim statistical reports based on the data safety and monitoring plan set forth in the protocol. It is possible that the study would be stopped and participants notified of the results and all participants would be offered the more effective drug combination.

GLOSSARY OF TERMS

Adverse event:

Any unanticipated problem involving risks to human research participants.

Adverse event reports:

Researcher reports of all serious and adverse events, injury and deaths given to the sponsor, the IRB, the FDA, and the NIH.

Assent:

Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Assurance:

Renewable permit granted by a Federal Department to an institution to conduct research in compliance with government standards.

Belmont Report:

Ethical Principles and Guidelines for the Protection of Human Participants of Research. Cornerstone document of ethical principles and Federal regulation of protection for research participants based on respect for persons, beneficence and justice. Applications of these three ethical principles to the conduct of research leads to consideration of required informed consent and privacy and confidentiality; risk/benefit assessment and scientific merit; and the selection of research participants.

Benefit:

A research benefit is considered to be something of health-related, psychological, or other value to an individual research participant, or something that will contribute to the acquisition of generalizable knowledge. Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

Certification:

The official notification by the institution to the supporting Department or Agency, in accordance with the requirements of 45CFR46, that a research project or activity involving human participants has been reviewed and approved by an Institutional Review Board in accordance with an approved assurance.

Children:

Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

Common Rule:

The Federal Policy for the Protection of Human Subjects was adopted in 1991 and covers research supported by the Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS as well as NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission. The provisions are identical to the DHHS Regulations (45 CFR 46, Subpart A).

Consent form:

Contains all relevant research information explained in lay terms and documents voluntary participation. Information includes a statement about potential risks and must address each of the eight elements required by the regulations. This is presented to and signed by the participant, and retained in the participant's medical record.

Data:

Information organized for analysis or used as the basis for decision-making.

Data and Safety Monitoring Board (DSMB):

An independent committee whose function it is to provide data and safety monitoring of a research study. DSMBs are required by NIH for all Phase III clinical trials, but may also be appropriate for Phase I and Phase II clinical trials if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.

Data and Safety Monitoring Plan:

A plan with a general description of data and safety monitoring of a research study. This is trial-specific, developed by the researcher, included in the protocol, and submitted to the IRB for review and approval before the study begins.

Declaration of Helsinki:

Statement of ethical principles first published in 1964 by the World Medical Association to define the rules for therapeutic and non-therapeutic research. In October 2000, revisions were made to the Declaration.

Department or Agency head:

The head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated.

Expected adverse event:

For approved and marketed drugs or devices, those adverse events described in the approved Package Insert (Label). For investigational new drugs or devices, those adverse events described in the FDA Investigator's Brochure. In clinical research studies, information on expected adverse events are summarized in the protocol and in the consent form.

Fetus:

The product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

Food and Drug Administration (FDA):

An agency within the Department of Health and Human Services (DHHS) that enforces the Food, Drug and Cosmetics Act and related Federal public health laws.

Guardian:

An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

Human participant (subject):

A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Inclusion criteria:

A list of criteria that must be met by all study participants.

Informed consent:

The process of information exchange between researcher and participant prior to written consent to participate in biomedical research. Information includes recruitment information, written materials as well as verbal instructions, questions and answer sessions about the research and its procedures. Participants are given the opportunity to choose research involvement based on information, comprehension, and willingness to volunteer.

Institutional Review Board (IRB):

An IRB established in accordance with and for the purposes expressed in 45CFR46 and 21CFR56. Insures that the data reported is credible and accurate and that the participant's rights and confidentiality are protected.

Institutional Review Board approval:

The determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

Interaction:

Includes communication or interpersonal contact between researcher and participant.

Intervention:

Includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes.

Institution:

Any public or private entity or Agency (including Federal, State, and other agencies); location of research. Has ultimate responsibility for human participation regulation compliance.

Legally authorized representative:

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to his/her participation in the procedure(s) involved in the research.

Minimal risk:

The probability and magnitude of harm or discomfort that is normally encountered in daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

National Institutes of Health (NIH):

The Federal Government's primary agency for advancing knowledge in biomedical and behavioral sciences in order to understand and treat human diseases. The NIH is part of the U.S. Public Health Service (PHS) which, in turn, is an agency within the DHHS.

National Research Act:

Created by the National Commission for Protection of Human Subjects of Biomedical and Behavioral research in 1974; mandated review of studies by institutional review boards and participant protection by informed consent.

Nuremberg Code:

Promulgated from the Nuremberg Doctor's Trial, the Code is a set of ten conditions to be met before research could be deemed ethically possible. This code became the first international standard for the conduct of research and began the modern era of protection for human research participants.

Office for Human Research Protection (OHRP):

This office interprets and oversees implementation of the regulations regarding the Protection of Human Participants codified at Title 45, Part 46, of the Code of Federal Regulations (45CFR46) promulgated by the DHHS. It is also responsible for providing guidance on ethical issues in biomedical and behavioral research. The OHRP has oversight and educational responsibilities wherever DHHS funds are used to conduct or support research involving human participants. It is located in the Office of the Secretary, Health and Human Services.

Office of Human Subjects Research (OHSR):

Promotes and supports NIH's Intramural Research Program's (IRP) efforts to conduct innovative research which protects the rights and promotes the welfare of human participants; assists IRP researchers in understanding and complying with the ethical guidelines and regulatory requirements of research involving human participants. Operates within the Office of the Deputy Director for Intramural Research (DDIR), National Institutes of Health (NIH).

Parent:

A child's biological or adoptive parent.

Permission:

The agreement of parent(s) or guardian to the participation of their child or ward in research.

Phase I trial:

A clinical trial that determines appropriate dose or intervention effect for use in a phase II or phase III trial. A phase I trial often enrolls only a small number of patients.

Phase II trial:

A clinical trial that continues to test the safety of the intervention, and begins to evaluate how well the intervention works.

Phase III trial:

A clinical trial that tests a new intervention in comparison to the current standard of care. A participant will frequently be assigned to a control group or the new intervention group at random (called randomization). Phase III trials often enroll large numbers of people and may be conducted at many doctors' offices, clinics, and centers nationwide.

Pregnancy:

Encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until the expulsion or extraction of the fetus.

Prisoner:

Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Private information:

Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the participant is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human participants.

Protocol:

Documentation of research objective, design, methods, statistical methods and organization; includes amendments made to the original document.

Recruitment:

The act of selecting and enrolling research participants with the proper inclusion criteria.

Research:

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of 45CFR46, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Researcher:

The individual who conducts and directs the study and carries the primary responsibility for research. The researcher is referred to as the Principle Investigator when acting as leader of a research team.

Risk-Benefit Analysis:

Risk (harm) to participant vs. potential benefits; also referred to as risk-benefit assessment.

Sponsor:

An individual, company, institution, or organization taking responsibility for initiation, management and financing of a research study.

Toxicity:

An adverse effect to an organ system and/or to the participant's subjective status produced by therapy. Toxicities are "graded" numerically, with the lowest number representing no toxicity (e.g., 0 = none) and the highest number highest representing lethal toxicity (e.g., 5 = lethal).

Unexpected adverse event:

That adverse event not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

Vulnerable participants/population:

Individuals/group that cannot give informed consent because of limited autonomy (e.g., children, mentally ill, prisoners), or who may be unduly influenced to participate (e.g., students, subordinates, terminally ill).

NMCP INSTRUCTIONS FOR INFORMED CONSENT

This section includes local instructions for the consenting process. Proper consenting of subjects is an essential part of ethical research. One of the three principles contained in the Belmont Report guiding the conduct of ethical research is "respect for persons". Informed consent is a process between the investigator and the subject to ensure that the subject is respected as an autonomous individual capable of making a decision regarding participation in research once he/she has the necessary information to make such a decision. Improper consent of subjects disregards the principle of respect for persons and may negate the use of data for the purpose of analysis and may result in suspension or termination of a study. This form is part of the NMCP Human Research protocol package. Principal investigators must ensure that if there are changes in investigators on the study (principal, associate or sub-investigators), new investigators read and sign the form.

Informed Consent Document Procedures

1. **The Investigator (PI, AI or Sub-I) along with a Witness (a disinterested adult, i.e. not affiliated with the research project and not a family member of the subject) will go together to talk with the prospective subject.** The Investigator will present and explain the research project to the prospective subject in the presence of the witness. This brief explanation will include the purpose and the nature of the research, the potential risks and benefits, an explanation of what is expected of the subject and for how long, along with alternatives to the research. If the prospective subject is interested proceed to step 2.

2. **The prospective subject will be given a copy of the informed consent document (ICD) to read and adequate time to read it.** The only acceptable alternative procedure would be for the Investigator to read the documents to the prospective subject in the presence of the witness. **The ICD must be a copy of the latest, IRB-Approved versions available and must contain the CIRD date-stamp and be initialed by CIRD Staff in order to be used.** Proceed to step 3.

3. **When the prospective subject has finished reading the ICD, the investigator and the Same witness will return together to discuss the research project and the document.** The investigator will ask the prospective subject if they have read the ICD and if they have, the investigator will ask them if they have any questions about the research project or the document. Once all the prospective subject's questions have been answered and if the prospective subject agrees to participate in the research project proceed to step 4.

4. **The investigator will have the subject or their representative initial every page of the ICD. Then the subject should print their name and SSN on the document, date and sign. The witness will then print their name, date and sign. Then the investigator will make sure all items are complete and that the dates are accurate then print their name on the ICD, date and sign it.** Proceed to step 5.

5. **The signed original ICD will be maintained by the Investigator and turned over to CIRD at the next scheduled Continuing Review. A copy of the ICD (which may be signed or unsigned) will be given to the subject or their representative for future reference.** A copy of the signed ICD may be maintained in a study file if the Principal Investigator desires or requires it.

6. **If a mistake is made, it should be corrected immediately by the person who made the mistake using the following procedure.** A single line should be drawn through the incorrect information and the correct information should be written next to the incorrect information. The person who made the mistake and the correction should initial the correction.

7. **Any exceptions to this policy must be approved in writing by the IRB.**

By signing below I certify that I have read and understand the ICD Procedures:

Typed/Printed Investigator Name	**Signature**

THE BELMONT REPORT

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare.

Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

*** *David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

****Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

*** *Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

*** *Deceased.*

Table of Contents

Ethical Principles and Guidelines for Research Involving Human Subjects

A. Boundaries Between Practice and Research

B. Basic Ethical Principles

1. Respect for Persons

2. Beneficence

3. Justice

C. Applications

1. Informed Consent

2. Assessment of Risk and Benefits

3. Selection of Subjects

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects. This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty.

Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.
Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.
While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

---

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual,

and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

National Institutes of Health
Bethesda, Maryland 20892

45 CFR PART 46
SUBPARTS A, B, D

immediately notify the Department that such an action is pending.

(e) The employee may, thereafter, request either (1) indemnification to satisfy a verdict, judgment or award entered against the employee or (2) payment to satisfy the requirements of a settlement proposal. The employee shall submit a written request, with documentation including copies of the verdict, judgment, award or settlement proposal, as appropriate, to the head of his employing component, who shall thereupon submit to the General Counsel, in a timely manner, a recommended disposition of the request. The General Counsel shall also seek the views of the Department of Justice. The General Counsel shall forward the request, the employing component's recommendation and the General Counsel's recommendation to the Secretary for decision.

(f) Any payment under this section either to indemnify a Department of Health and Human Services employee or to settle a personal damage claim shall be contingent upon the availability of appropriated funds of the employing component of the Department of Health and Human Services.

(Authority: 5 U.S.C. 301)

[53 FR 11280, Apr. 6, 1988]

PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Sec.

46.101 To what does this policy apply?
46.102 Definitions.
46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
46.104–46.106 [Reserved]
46.107 IRB membership.
46.108 IRB functions and operations.
46.109 IRB review of research.
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
46.111 Criteria for IRB approval of research.
46.112 Review by institution.
46.113 Suspension or termination of IRB approval of research.
46.114 Cooperative research.
46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

46.201 Applicability.
46.202 Purpose.
46.203 Definitions.
46.204 Ethical Advisory Boards.
46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.
46.206 General limitations.
46.207 Activities directed toward pregnant women as subjects.
46.208 Activities directed toward fetuses in utero as subjects.
46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.
46.210 Activities involving the dead fetus, fetal material, or the placenta.
46.211 Modification or waiver of specific requirements.

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

46.301 Applicability.
46.302 Purpose.
46.303 Definitions.
46.304 Composition of Institutional Review Boards where prisoners are involved.
46.305 Additional duties of the Institutional Review Boards where prisoners are involved.
46.306 Permitted research involving prisoners.

Subpart D—Additional Protections for Children Involved as Subjects in Research

46.401 To what do these regulations apply?
46.402 Definitions.
46.403 IRB duties.

46.404 Research not involving greater than minimal risk.
46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
46.408 Requirements for permission by parents or guardians and for assent by children.
46.409 Wards.

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289.

EFFECTIVE DATE NOTE: At 66 FR 3882, Jan. 17, 2001, the authority for part 46 was revised, effective Mar. 19, 2001. At 66 FR 15352, Mar. 19, 2001, the effective date was delayed until May 18, 2001, and at 66 FR 27599, May 18, 2001, the effective date was further delayed until Nov. 14, 2001. For the convenience of the user, the revised text is set forth as follows:

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289(a).

EDITORIAL NOTE: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost—sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289, 42 U.S.C. 300v–1(b).

SOURCE: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic,

aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research

Risks, Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§ 46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

---

[1] Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A–D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with §46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and

approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under control number 9999–0020)

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§§46.104—46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in § 46.103(b)(4) and, to the extent required by, § 46.103(b)(5).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under control number 9999–0020)

§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described is §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

(Approved by the Office of Management and Budget under control number 9999–0020)

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the

purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

(Approved by the Office of Management and Budget under control number 9999–0020)

§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under control number 9999–0020)

§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragarph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

SOURCE: 40 FR 33528, Aug. 8, 1975, unless otherwise noted.

EFFECTIVE DATE NOTE: At 66 FR 3882, Jan. 17, 2001, subpart B was revised, effective Mar. 19, 2001. At 66 FR 15352, Mar. 19, 2001, the effective date was delayed until May 18, 2001, and at 66 FR 27599, May 18, 2001, the effective date was further delayed until Nov. 14, 2001. For the convenience of the user, subpart B effective Nov. 14, 2001, follows the text of this subpart B.

§46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving:

(1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *Pregnancy* encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) *Fetus* means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) *Viable* as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) *Nonviable fetus* means a fetus *ex utero* which, although living, is not viable.

(f) *Dead fetus* means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) *In vitro fertilization* means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the

Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978; 59 FR 28276, June 1, 1994]

§46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in §46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

[40 FR 33528, Aug. 8, 1975, as amended at 46 FR 8386, Jan. 26, 1981]

§46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

[40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

§46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

EFFECTIVE DATE NOTE: At 66 FR 3882, Jan. 17, 2001, subpart B was revised, effective Mar. 19, 2001. At 66 FR 15352, Mar. 19, 2001, the effective date was delayed until May 18, 2001, and at 66 FR 27599, May 18, 2001, the effective date was further delayed until Nov. 14, 2001. For the convenience of the user, the revised text is set forth as follows:

Subpart B—Additional Protections for Pregnant Women and Human Fetuses Involved in Research, and Pertaining to Human In Vitro Fertilization

§ 46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women or human fetuses, and to all research involving the in vitro fertilization of human ova, conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at § 46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of § 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in § 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Definitions.

The definitions in § 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Dead fetus* means a fetus after delivery that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord. Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(b) *Fetus* means the product of conception from implantation until a determination is made after delivery that it is viable.

(c) *In vitro fertilization* means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

(d) *Nonviable fetus* means a fetus after delivery that, although living, is not viable.

(e) *Pregnancy* encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(f) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(g) *Viable* as it pertains to the fetus means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus after delivery is viable then it is a child as defined by § 46.402(a), and subpart D of this part is applicable.

§ 46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and human in vitro fertilization.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§ 46.204 Research involving pregnant women or fetuses prior to delivery.

Pregnant women or fetuses prior to delivery may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) The woman's consent or the consent of her legally authorized representative is obtained in accord with the informed consent provisions of subpart A of this part, unless altered or waived in accord with § 46.101(i) or § 46.116(c) or (d);

(e) The woman or her legally authorized representative, as appropriate, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child;

(f) For children as defined in 45 CFR 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(g) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(h) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(i) Individuals engaged in the research will have no part in determining the viability of a fetus.

§ 46.205 Research involving fetuses after delivery.

(a) After delivery, fetuses may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to fetuses.

(2) The individual(s) providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child.

(3) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

(4) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

(5) Individuals engaged in the research will have no part in determining the viability of a fetus.

(6) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Fetuses of uncertain viability. After delivery, and until it has been ascertained whether or not a fetus is viable, a fetus may not be involved in research covered by this subpart unless the following additional conditions are met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the particular fetus to the point of viability, and any risk is the least possible for achieving the objectives of the research, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the fetus resulting from the research; and

(2) The legally effective informed consent of either parent of the fetus or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, unless altered or waived in accord with § 46.101(i) or § 46.116(c) or (d).

(c) Nonviable fetuses. After delivery, a nonviable fetus may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the fetus will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the fetus;

(3) There will be no risk to the fetus resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the fetus is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of § 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable fetus will suffice to meet the requirements of this paragraph. The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice to meet the requirements of this paragraph.

(d) Viable fetuses. A fetus, after delivery, that has been determined to be viable is a child as defined by § 46.402(a) and may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§ 46.206 Research involving, after delivery, the placenta, the dead fetus, or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§ 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of § 46.204 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women or fetuses; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable, or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women or fetuses;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d).

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

SOURCE: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8386, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the published notice, in the FEDERAL REGISTER, of his intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D—Additional Protections for Children Involved as Subjects in Research

SOURCE: 48 FR 9818, Mar. 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

[48 FR 9818, Mar. 8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991]

§46.402 Definitions.

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

PART 50—U.S. EXCHANGE VISITOR PROGRAM—REQUEST FOR WAIVER OF THE TWO-YEAR FOREIGN RESIDENCE REQUIREMENT

Sec.
50.1 Authority.
50.2 Exchange Visitor Waiver Review Board.
50.3 Policy.
50.4 Procedures for submission of application to HHS.
50.5 Personal hardship, persecution and visa extension considerations.
50.6 Release from foreign government.

AUTHORITY: 75 Stat. 527 (22 U.S.C. 2451 et seq.); 84 Stat. 116 (8 U.S.C. 1182(e)).

SOURCE: 49 FR 9900, Mar. 16, 1984, unless otherwise noted.

§50.1 Authority.

Under the authority of Mutual Educational and Cultural Exchange Act of 1961 (75 Stat. 527) and the Immigration and Nationality Act as amended (84 Stat. 116), the Department of Health and Human Services is an "interested United States Government agency" with the authority to request the

32 CFR PART 219

examined. Typical sources of error include orientation of the weapons, specific weapon yields, instrument error, fallout intensity data, time(s) at which data were obtained, fallout decay rate, route of personnel movements, and arrival/stay times for specific activities.

(f) *Comparison with film badge records.* (1) Calculations of gamma dose were compared with film badge records for two military units at Operation PLUMBBOB to initially validate this methodology. Where all parameters relating to radiation exposure were identified, direct comparison of gamma dose calculations with actual film badge readings was possible. Resultant correlations provided high confidence in the methodology.

(2) Film badge data may, in some cases, be unrepresentative of the total exposure of a given individual or group; nevertheless, they are extremely useful for direct comparison of incremental doses for specific periods, e.g., validating the calculations for the remaining, unbadged period of exposure. Moreover, a wide distribution of film badge data often leads to more definitive personnel grouping for dose calculations and to further investigation of the reason(s) for such distribution. In all cases, personnel film badge data are not used in the dose calculations, but rather are used solely for comparison with and validation of the calculations. For dose reconstructions accomplished to date, comparison has been favorable and within the confidence limits of the calculations.

§ 218.4 Dose estimate reporting standards.

The following minimum standards for reporting dose estimates shall be uniformly applied by the Military Services when preparing information in response to an inquiry by the Veterans Administration, in connection with a claim for compensation, or by a veteran or his or her representative. The information shall include all material aspects of the radiation environment to which the veteran was exposed and shall include inhaled, ingested, and neutron doses, when applicable. In determining the veteran's dose, initial neutron, initial gamma, residual gamma, and internal (inhaled and ingested) alpha, beta, and gamma shall be considered. However, doses will be reported as gamma dose, neutron dose, and internal dose. To the extent to which the information is available, the responses will address the following questions:

(a) Can it be documented that the veteran was a test participant? If so, what tests did he attend and what were the specifics of these tests (date, time, yield (unless classified) type, location and other relevant details)?

(b) What unit was the man in? What were the mission and activities of the units at the test?

(c) To the extent to which the available records indicate, what were his duties at the test?

(d) Can you corroborate the specific information relevant to the potential exposure provided by the claimant to the Veterans Administration and forwarded to the Department of Defense? What is the impact of these specific activities on the claimant's reconstructed dose?

(e) Is there any recorded radiation exposure for the individual? Does this recorded exposure cover the full period of test participation? What are the uncertainties associated with the recorded film badge dose?

(f) If recorded dosimetry data is unavailable or incomplete, what is the dose reconstruction for the most probable dose, with error limits, if available?

(g) Is there evidence of a neutron or internal exposure? What is the reconstruction?

Upon request, the participant or his or her authorized representative will be informed of the specific methodologies and assumptions employed in estimating his or her dose.

PART 219—PROTECTION OF HUMAN SUBJECTS

Sec.
219.101 To what does this policy apply?
219.102 Definitions.
219.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
219.104—219.106 [Reserved]
219.107 IRB membership.
219.108 IRB functions and operations.
219.109 IRB review of research.

219.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
219.111 Criteria for IRB approval of research.
219.112 Review by institution.
219.113 Suspension or termination of IRB approval of research.
219.114 Cooperative research.
219.115 IRB records.
219.116 General requirements for informed consent.
219.117 Documentation of informed consent.
219.118 Applications and proposals lacking definite plans for involvement of human subjects.
219.119 Research undertaken without the intention of involving human subjects.
219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
219.121 [Reserved]
219.122 Use of Federal funds.
219.123 Early termination of research support: Evaluation of applications and proposals.
219.124 Conditions.

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

SOURCE: 56 FR 28012, 28021, June 18, 1991, unless otherwise noted.

§ 219.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in § 219.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in § 219.102(e) must be reviewed and approved, in compliance with § 219.101, § 219.102, and § 219.107 through § 219.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such

a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies,

(i) If wholesome foods without additives are consumed or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28021, June 18, 1991, as amended at 56 FR 29756, June 28, 1991]

---

[1] Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A–D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro

§219.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

---

fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

§219.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §219.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with §219.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this

policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §219.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §219.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §219.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under control number 9999–0020)

[56 FR 28012, 28021, June 18, 1991, as amended at 56 FR 29756, June 28, 1991]

§§ 219.104—219.106 [Reserved]

§ 219.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 219.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in § 219.103(b)(4) and, to the extent required by, § 219.103(b)(5).

(b) Except when an expedited review procedure is used (see § 219.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ 219.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 219.116. The IRB may require that information, in addition to that specifically mentioned in § 219.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 219.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 219.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §219.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§219.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §219.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §219.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§219.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§219.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 219.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§ 219.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described is § 219.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in § 219.103(b)(4) and § 219.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by § 219.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 219.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(i) Public benefit of service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 219.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 219.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by § 219.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under control number 9999–0020)

§ 219.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under § 219.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§ 219.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§219.121 [Reserved]

§219.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§219.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragarph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§219.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

PART 220—COLLECTION FROM THIRD PARTY PAYERS OF REASONABLE COSTS OF HEALTHCARE SERVICES

Sec.

220.1 Purpose and applicability.
220.2 Statutory obligation of third party payer to pay.
220.3 Exclusions impermissible.
220.4 Reasonable terms and conditions of health plan permissible.
220.5 Records available.
220.6 Certain payers excluded.
220.7 Remedies and procedures.
220.8 Reasonable costs.
220.9 Rights and obligations of beneficiaries.
220.10 Special rules for Medicare supplemental plans.
220.11 Special rules for automobile liability insurance and no-fault automobile insurance.
220.12 Special rules for preferred provider organizations.
220.13 Special rules for workers' compensation programs.
220.14 Definitions.

AUTHORITY: 5 U.S.C. 301; 10 U.S.C. 1095.

SOURCE: 55 FR 21748, May 29, 1990, unless otherwise noted.

§220.1 Purpose and applicability.

This part implements the provisions of 10 U.S.C. 1095. In general, 10 U.S.C. 1095 establishes the statutory obligation of third party payers to reimburse the United States the reasonable costs

10 USC SECTION 980

There are two primary limitations on DoD research implied by 10 USC 980. The first is that there will be no research on potential subjects who by virtue of their medical condition cannot give informed consent. Examples would be patients in cardiac arrest in transport to a medical facility (or some other emergency situation). There are federal guidelines for conducting this type of research, but it cannot be conducted in DoD institutions.

The second limitation is that with respect to research involving children, there must be the prospect of direct benefit to the child. This has been interpreted to exclude clinical trial research involving children that includes a control and/or placebo group that does not receive any treatment. The memo of 25 September, 2000 addresses this issue.

-CITE-

10 USC Sec. 980 01/26/98

-EXPCITE-

TITLE 10 - ARMED FORCES

Subtitle A - General Military Law

PART II - PERSONNEL

CHAPTER 49 - MISCELLANEOUS PROHIBITIONS AND PENALTIES

-HEAD-

Sec. 980. Limitation on use of humans as experimental subjects

-STATUTE-

Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless -

(1) the informed consent of the subject is obtained in advance; or

(2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance.

-SOURCE-

(Added Pub. L. 98-525, title XIV, Sec. 1401(c)(1), Oct. 19, 1984, 98 Stat. 2615.)

September 25, 2000

MEMORANDUM FOR THE DIRECTOR, NAVY CLINICAL INVESTIGATION PROGRAM

SUBJECT: Application of 10 U.S.C. 980 in the Context of Controlled Clinical Investigations Involving Children

This responds to your request for clarification regarding the Department's legal obligations under 10 U.S.C. 980 in the context of controlled clinical investigations involving children. You referred to a legal opinion of October 2, 1997.

10 U.S.C. 980 provides:

> Funds appropriated to the Department of Defense may not be used for research involving a human being as a experimental subject unless--
>
> (1) the informed consent of the subject is obtained in advance; or
>
> (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance.

The 1997 opinion was in response to a general question about whether, for purposes of allowing informed consent by a legal representative under section 980, research would be "intended to be beneficial" to children in a placebo control group arm of a research project. The opinion advised because there would be no apparent intended benefit to a subject in a control group, consent by a legal representative would not appear to be authorized. This was in response to a general question, unrelated to any particular proposed research project. The response assumed no other pertinent facts.

The request for clarification assumes additional facts not presented in relation to the 1997 opinion. The additional facts are that particular research projects may offer benefit to subjects in both the active arm and control arm. This is an important difference; the 1997 opinion was not intended to infer that subjects in control arms could never benefit from participation in research studies. In actual research projects, subjects in the control arm may receive much more than a placebo.

The requirement of section 980 is that informed consent of a legal representative is permissible "in the case of research intended to be beneficial to the subject." The statute does not elaborate further regarding the nature of the benefit. It is my view that the most defensible approach to this issue is to look to the Institutional Review Board to consider whether the proposed research is in fact intended to be beneficial to all subjects, including those in the control arm. If the IRB finds that it is so intended, the command of section 980 can be met through the informed consent of a legal representative.

Your suggestion that clarification on this point is needed is well taken. I have suggested to the Office of the Director of Defense Research and Engineering that appropriate guidance be included in the upcoming update to DoD Directive 3216.2, "Protection of Human Subjects in DoD-Supported Research," January 7, 1983.

I hope you find this responsive to your request. If anything further is required, please advise.

//Signed//

John A. Casciotti
Associate Deputy General Counsel
(Health Affairs)